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EXPLORATIONS ON THE TOXICOLOGICAL POTENTIAL OF ZINC AND COPPER NANOCOMPOUNDS

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ABSTRACT
Nanoparticles (NPs) represent one of the most extensively studied topics today, as their increasing use across various fields of human activity necessitates an evaluation of their toxicological profile. Zinc (Zn) and copper (Cu) nanoparticles are increasingly studied because of their antimicrobial properties, role in plant nutrition and resilience, and potential applications in drug delivery. However, concerns persist regarding their environmental impact and biological toxicity, which depend on factors such as synthesis method, concentration, and exposure conditions. This study explores the toxicological potential of Zn and Cu NPs, their effects on plants and microorganisms, and their potential future applications, aiming to contribute to a deeper understanding of nanoparticle safety and sustainability.
KEY WORDS: *nanoparticles, zinc, copper, toxicity, environmental impact, nanotechnology*

INTRODUCTION

The scientific literature defines the concept of nanomaterials in various ways, but among the most explicit is the general concept that they are materials smaller than 100 nm in size. Defining the concept in a more particularly way, nanomaterials exhibits specific characteristics in correlation with their size (Vollath, 2008).

Given their unique and abundant properties – their catalytic qualities, surface treatment applications, and function in energy conversion and storage (Goesmann & Feldmann, 2010) – nanoparticles have started to be considered as possible substitutes for traditional antibiotics. Moreover, some nanoparticles can be used as components of certain medical devices, due to their specific physical and biological properties (Datcu & Ciobanu, 2020).

An additional direction in which nanoparticles could be used is heritage preservation. Studies done by Corbu *et al* (2023) emphasized that silver, copper, zinc oxide, and gold nanoparticles could be of use as an alternative for heritage preservation as a result of their antimicrobial properties against biodeteriogenic strains. Moreover, nanoparticles like magnesium diboride, could help preserve cultural heritage objects considering their antifungal properties, as demonstrated by Gheorghe *et al* (2021).

Extensive research is available on various materials, especially metals, such as gold, platinum, silver, zinc, copper (Azam *et al*, 2009; Gordon *et al*, 2011; Aygun *et al*, 2020; Bruna *et al*, 2021) and their synthesis method, as well as antibacterial properties (Khandel *et al*, 2018). However, there is a prevalent need for extensive research regarding their potential toxicity on animals and plants (Mathur *et al*, 2023; Xuan *et al*, 2023).

1. GENERAL ASPECTS

Zinc nanoparticles

Zinc is a fundamental micronutrient that modulates the process of plant growing and development, being absorbed from the soil or aqueous solutions through leaves or roots in the form of soluble Zn^{2+} ions or as chelates of organic acids (Palmgren *et al*, 2008; Doolette *et al*, 2018).

At the cellular level, zinc is involved in maintaining cell membrane integrity, protein synthesis, and carbohydrate metabolism, playing a key role in regulating auxin levels and pollen formation (Umair Hassan *et al*, 2020). Due to its low solubility, zinc often presents deficiencies in soils and plants, leading to reduced growth and increased susceptibility of plants to biotic and abiotic stress, which is frequently manifested by chlorotic spots and a decrease in leaf surface area (Gondal, 2021).

Available approaches to correct zinc deficiency include the use of conventional chemical fertilizers, mobilization of existing soil zinc through the application of zinc-solubilizing bacterial strains, as well as alternative methods. However, the latter solutions are often overlooked in agricultural practice due to their insufficient efficiency in meeting the demands of present-day agriculture (Rani *et al*, 2020). Although widely used, most agrochemicals show low efficiency, failing to reach the target in satisfactory amounts due to post-application processes such as hydrolysis, leaching, or degradation by soil microorganisms (Ortiz-Hernández *et al*, 2013).

Nanoforms of pesticides and fertilizers have demonstrated high application potential, allowing for a more efficient and controlled delivery of biologically active substances (Pramanik *et al*, 2020). Because of their unique size and characteristics, plants are capable of absorbing those nanoforms at a higher rate and at significantly lower concentrations than conventional bulk forms (Sabir *et al*, 2014).

One of the most commonly used nanoforms are zinc nanoparticles, due to their potential to alleviate plant biotic stress and their antimicrobial properties (Ansari *et al*, 2018). Being widely available, cost-effective, and having good stability under various environmental conditions, Zn NPs are used both to correct soil zinc deficiencies and for the targeted transport of drugs and nutrients (Sturikova *et al*, 2018).

Copper nanoparticles

Due to its high availability and abundance, copper is one of the most widely used metals in anthropogenic activities, being valued for its various particularities, such as excellent thermal and electrical conductivity, high malleability, and strong resistance to corrosion (Vimbela *et al*, 2017).

In living organisms, copper plays an essential role in cellular metabolism, being a component of over 30 types of proteins, predominantly found in the skin, bones, and other organs. Cupric enzymes participate in several fundamental processes of animal organisms, including iron homeostasis and the transport of respiratory gases (Vimbela *et al*, 2017; Al-Hakkani, 2020).

In plants, copper supports growth and development processes by participating in cellular respiration, electron transport from photosynthesis, protein regulation, and cell membrane metabolism (Crisan *et al*, 2021). Copper deficiency is often manifested by leaf wilting and curling, while excessive copper can inhibit growth and photosynthesis, leading to toxicity and oxidative stress (Shobha *et al*, 2014).

With remarkable mechanical, thermal, magnetic, and electrical properties, copper nanoparticles have become a major focus in scientific research, being employed in the creation of antimicrobial coatings for surgical instruments, water treatment applications, and the fabrication of thermal transfer systems (Mohamed, 2020).

2. NANOPARTICLES SYNTHESIS

The synthesis of nanoparticles is influenced by a series of direct and indirect factors, from the selected synthesis pathway and the available physiological conditions, such as medium pH, temperature, and reaction time, to the type of metal ion precursors used and the microbial species involved in the biosynthesis (Patra & Baek, 2015). The shape, dimension, and stability of the resulting nanoparticles are directly influenced by the variations of these parameters, which ultimately determine their specific properties.

The main synthesis methods and their corresponding characteristics are presented in Table 1.

TABLE 1. The main synthesis pathways of zinc and copper NPs

Method	Pathway	Characterization	References
Conventional	physical	-through ultrasonication, laser ablation, electromagnetic wave irradiation. -requires highly sophisticated instrumentation. -involves high costs. - NPs acquired through physical synthesis are not contaminated by their solvent and present a uniform distribution, thus improving the outcome quality compared to chemical synthesis.	Iravani *et al*, 2014; Patel *et al*, 2015; Jameel *et al*, 2020.
	chemical	-through pyrolysis, solvothermal synthesis, chemical reduction, photochemical reduction, hydrothermal synthesis, etc. -requires high number of steps. -involves issues regarding the toxicity and lack of biodegradability of the chemicals utilized in the procedure.	Giannousi *et al*, 2014; Khandel *et al*, 2018; Salem & Fouda, 2021.
Biogenic	plant-mediated	- the obtained atoms combine and create small clusters that continue to develop into particles- there are no reduction factors required since they are already present in the plant extract used for NPs synthesis. -could help address agricultural waste issues since these materials can be processed to synthesize NPs -is cost-effective. -environmentally friendly.	Bankar *et al*, 2010; Thiruvengadam *et al*, 2019; Asghar & Asghar, 2020; Ishak *et al*, 2021.
	microorganism-mediated	- NPs are created through the oxidation/reduction (O/R) of metal ions by enzymes, proteins, and sugars - it can be done using intracellular pathways or extracellular pathways - controlling and manipulating the form and dimension of NPs is achievable to create the desired NPs, appropriate for particular applications	Zhang *et al*, 2011; Makarov *et al*, 2014; Salem & Fouda, 2021;

3. EFFECTS OF ZINC AND COPPER NPs ON ORGANISMS

Plants

Plant growth and productivity are strongly affected by drought, which negatively impacts seed germination, photosynthesis rate, leaf turgor, transpiration rate, nutrient translocation, and the production and depositation of ROS (reactive oxygen species), among other processes (Rani *et al*, 2020). The application of ZnO NPs, in various concentrations and modes, shows significant potential in mitigating the effects of water stress on plants. However, there is no clear consensus regarding the optimal administration method (Rani *et al*, 2021). Overall, NPs used in agriculture have the potential to provide a higher plant biomass and mitigate soil requirements (Ciobanu, 2019).

Among the most common uses of nanoparticles in agriculture is soil enrichment, especially with ZnO, leading to the fortification of indispensable nutrients such as Zn, N, K, Fe, and P (Dimkpa *et al*, 2019). Foliar application is another promising method, considered more controllable than solid fertilizers and capable of mitigating the symptoms associated with toxicty caused by soil application (Kah *et al*, 2018). ZnO nanoparticles have also been used as seed priming agents, showing significant positive effects on plant development. A distinct advantage of this method is the reduced amount of nanoparticles required, which lowers production costs and their environmental impact (Khalid *et al*, 2021).

Bacteria

Specialized studies have focused on several types of metal nanoparticles with antimicrobial properties, among the most frequently investigated being gold, silver, and copper NPs (Ramazanzadeh *et al*, 2015). Due to their ability to simultaneously interact with multiple biomolecules, nanoparticles can inhibit or even halt the development of resistant bacteria (Slavin *et al*, 2017). The scientific literature suggests that Gram-positive bacteria exhibit greater resistance to the action of nanoparticles, a phenomenon explained by structural differences in their cell walls (Crisan *et al*, 2021). In contrast, Gram-negative bacteria present an additional outer layer of lipopolysaccharides, which gives the cell surface a negative charge, favoring the attraction of positively charged ions released by nanoparticles. This interaction facilitates nanoparticle accumulation and penetration into the cell, ultimately damaging intracellular structures (Slavin *et al*, 2017).

Due to their economical accessibility, physicochemical stability, and compatibility with polymeric materials, there is often a comparation made between silver and cooper nanoparticles. (Bruna *et al*, 2021). Copper has been identified by the United States Environmental Protection Agency as the first solid substance to exhibit antimicrobial properties, in the context of its use in wound and water sterilization processes (Sistemática *et al*, 2016). The antibacterial efficacy of Cu and Zn NPs has also been confirmed by other studies, particularly against *Streptococcus mutans*, with promising results achieved even at low toxic concentrations (Ramazanzadeh *et al*, 2015).

Fungi

Copper has long been used as a base compound in the production of chemical fertilizers, pesticides, and fungicides. With the growing interest in nanotechnology, the use of copper nanoforms has demonstrated high fungicidal efficiency against numerous phytopathogens *(Fusarium oxysporum, Alternaria alternata, Penicillium digitatum, Penicillium italicum, Phoma destructiva, Rhizoctonia solani,* and *Curvularia lunata)* (Pariona *et al*, 2019).

4. NANOPARTICLES TOXICITY

There is an extensive literature base regarding both zinc and copper nanoparticles, in relation to the potential toxic effects that their use may have on the organisms themselves and/or on the environment. A relevant example is the study by Xu *et al* (2018), which shows that ZnO NPs can affect certain bacterial lines in the rhizosphere community to a greater extent than the conventional forms of these compounds. In a review study from 2020, it has been highlighted the importance of phytotoxicity tests application in order to establish the degree of NPs toxicity (Alexan, 2020). Several studies indicate that ZnO nanoparticles and their bulk forms exhibit similar toxicity levels. These findings highlight the need for undertaking of targeted studies, leading to the establishment of clear statistical evidence on the potential toxic effects of NPs (Rani *et al*, 2022). Amoung cytotoxic mechanisms already determined, one of the most common is the production of ROS and the induction of oxidative stress, phenomena that can damage cells exposed to nanoparticles (Yang *et al*, 2009). As an example, small amounts of CuO NPs are capable of generating large amounts of ROS, such as O_2^-, OH and H_2O_2, triggering their production and affecting the integrity of the cell membrane after entering the mitochondria (Xia *et al*, 2007).

5. PROSPECTIVE ADVANCEMENTS IN THE APPLICATION OF NANOPARTICLES

Toxicity studies on the two substances confirmed their beneficial properties, their observed adverse effects being linked to factors such as the nanoparticle synthesis method, concentration, exposure environment, and route of exposure. Both Zn and Cu nanoparticles have proven to be more harmful than their conventional form due to their high concentration and high solubility potential, organisms showing adverse effects when the optimal application concentrations are exceeded, depending on the method used and their solubility in the environment (Crisan *et al*, 2021; Rani *et al*, 2022). Regarding the method of synthesis of nanoparticles, due to the production costs and resources involved, chemical synthesis is still the most used in this regard, the use of chemical precursors, toxic to organisms and the environment, showing its negative impact (Lee *et al*, 2013; Patel *et al*, 2015).

Zinc nanoparticles

There is limited information available regarding the bacterial-mediated synthesis of nanoparticles. The specialized literature emphasizes the need to deepen the understanding of both intra- and extracellular mechanisms involved in their biosynthesis, as well as to identify the reducing and stabilizing agents participating this specific biological processes, with the aim of optimizing potential industrial-scale production and minimizing the influence of exogenous factors on nanoparticle biosynthesis (Salem & Fouda, 2021; Rani *et al*, 2022). Due to the necessity for a sterile environment and precise maintenance conditions, large-scale biosynthesis of NPs is not currently viable. (Dhuper *et al*, 2012).

The study of ZnO nanoparticle biosynthesis mediated by bacteria can be conducted through a detailed analysis of the total biomass filtrate obtained, thus permitting the identification and characterisation of the metabolites involved in the process. These compounds can potentially yield relevant insights into the molecular and biochemical aspects of synthesis, facilitating the selection of new microorganisms with enhancing potential for nanoparticle biosynthesis optimization (Yusof *et al*, 2019). A critical assessment of the benefits and risks associated with NP-based agricultural products is absolutely necessary, particularly when considered in relation to conventional agrochemicals whose effects are already well documented (Kah *et al*, 2018).

Copper nanoparticles

Studies conducted on copper nanoparticles have highlighted their antibacterial potential, demonstrating high efficacy against a broad range of pathogenic species. As such, these compounds hold considerable promise for further use and development, being valuable both as biocides/bacteriocides in agriculture and as potential substitutes for antibiotic treatments in the medical field (Kalińska *et al*, 2019). However, given their toxic potential, a thorough evaluation of safe application methods for copper nanoparticles is necessary (Xia *et al*, 2007).

In the agricultural sector, copper nanoparticles have shown a possible beneficial effect on crops such as wheat, indicating their potential use as biostimulant agents aimed at improving agricultural yields and responding to the continuously increasing global food demand. Nevertheless, comprehensive research is required to ascertain the optimal application method as well as the appropriate exposure duration for plants (Hafeez *et al*, 2015).

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